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10/050,200	01/16/2002	Anne M. Fourie	ORT-1417	6279

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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PA 1/16/2002

7-13

20-21

Office Action Summary

Application No.

10/050,200

Applicant(s)

FOURIE ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 7-19 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-9 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: .

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The Application is acknowledged. Claims 1-19 are pending; claims 1-7 are the subject of this Office Action. Claims 1-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

DETAILED ACTION

1. Restriction/election

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claim 1-6, drawn to polypeptides being aggrecanase substrates, wherein the aggrecanase is set forth by SEQ ID NO: 8 and 9, classified in class 530, subclass 300.
- II. Claim 7-19 a method for identifying a compound that inhibits aggrecanase activity; classified in class 435, subclass 23.

Inventions of Group I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process, a method for identifying a compound that inhibits aggrecanase activity can be practiced with a substrate that is more than 40 amino acid long.

Inventions of Groups I and II are distinct for the reason given above and have acquired a separate status in the art. Because of their recognized divergent subject

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matter and/or different classification, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Applicants' representative Myra H. McCormack on March 11, 2003, a provisional election was made without traverse to prosecute the invention of Group II, claims 7 -19 ~~14~~. Affirmation of this election must be made by Applicant in replying to this Office Action.

Claims 1-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Objections

2.1. Specification

The specification is objected to for wrong and inconsistent spelling of the name aggrecanase. The name should start with small letter a. The numbering of the enzyme used by the Applicants is aggrecanase -1 and aggrecanase-2, e.g. page 1, or aggrecanase 1 and aggrecanase 2, e.g. page 10. The spelling used in the art is aggrecanase-1 and aggrecanase-2.

The specification is objected to for confusing use of the terms aggrecanase-1 and -2. On page 1, line 29, by the terms aggrecanase-1 and -2 Applicants mean the full-length aggrecanases that cleave aggrecan. The description given on page 2 is as follows: "sequence of SEQ ID NO: 8 (Aggrecanase-1) and/or SEQ ID NO: 9 (Aggrecanase-2)", whereas SEQ ID NOs: 8 and 9 are the truncated forms of aggrecanase-1 and aggrecanase-2. Applicants are requested to correct the specification and use the term truncated aggrecanase-1 or aggrecanase of SEQ ID NO: 8, and truncated aggrecanase-2 or aggrecanase of SEQ ID NO: 9 when they mean the polypeptides of the invention, and use the names aggrecanase -1 and aggrecanase -2 for the full-length enzymes disclosed in prior art.

The abbreviation MMPs on page 1, line 31, should be expanded.

The abbreviation HTS on page 2, line 23, should be expanded.

The abbreviation FRET that is used for the first time in the specification on page 5, line 2, should be expanded.

Page 7, line 20 refers the reader to table II to see other peptides. The table referred to should be Table III. Please note the discrepancy in the table numerals between the text and actual table title. In the text the numerals are Roman, and in the table titles they are Arabic.

Table 3 is objected to for lack of explanations for the terms: Aedans, and (Dabacyl)K-amide.

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The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

2.2. Claims

The term aggrecanase should be written starting with small letter a.

2.2. Drawings

Fig. 2 is described on page 5 as illustration of "relative activities" of aggrecanase -1(A) and -2 (B) for 56 different FRET peptides. It is unknown what Applicant mean by relative activities; relative to what? On page 16, line 5, Applicants write "expressed in arbitrary, but relative units", which is still unclear.

Fig. 2 misses description of y-axis.

3. Rejections

3.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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Claim 7-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is unclear in reciting "an amino acid sequence corresponding to SEQ ID NO: 8 and /or SEQ ID NO: 9". The term "corresponding to a sequence" is not defined in the claim or specification. Therefore, it is unknown what Applicants mean by ^{de} ~~written~~ corresponding to SEQ ID NO: 8 and /or SEQ ID NO: 9." The phrase "an amino acid sequence corresponding to SEQ ID NO: 8 and/or SEQ ID NO: 9" renders claim 7 and dependent claims indefinite. For examination purposes it is assumed that Applicants mean any aggrecanase.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 7 -19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7-9 and 11-13 are directed to a method of use of a large and variable genus of peptides that are less than 40 amino acids in length wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side of the polypeptides. Applicants disclose several representatives of the claimed genus identified by SEQ ID NOs: 3, 4, 5, 6 and 7. This is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants fail to disclose any particular structure to function (of being cleavable by the truncated aggrecanase -1 and -2, i.e., SEQ ID NO: 8 and 9 or by any aggrecanase) relationship for a polypeptide that is less than 40 amino acids in length, wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side of said polypeptide.

No information, beyond the characterization of SEQ ID NO: 3, 4, 5, 6 and 7 has been provided by Applicants, which would indicate that they had possession of the claimed genus of these polypeptides. The data presented in Fig. 2 clearly prove that predictability of the function of the representatives of the claimed genus is not apparent. The fact that a polypeptide of less than 40 amino acid long comprises a glutamic acid and as a neighbor on the C-terminal side of said glutamic acid a non-polar or uncharged amino acid is not sufficient for the polypeptide to be cleavable by SEQ ID

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NO: 8 or 9. In addition, it is even less apparent which of such polypeptides are the substrates for any aggrecanase.

Given the lack of structural characteristics of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claims 7-8, 10-13, 17 and 19 are directed to a method ^{of} using any aggrecanase, because the claims recite the term aggrecanase or a polypeptide "corresponding to SEQ ID NOs: 8 and /or SEQ ID NO: 9." Applicants disclose two representatives of truncated forms of aggrecanase-1 and -2 set forth by amino acid sequence of SEQ ID NO: 8 and 9. This is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants fail to disclose any particular structure to function relationship identifying the claimed genus of polypeptides. Given the lack of structural characteristics of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

2.2.2. Scope of invention

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Claim 7–19 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the polypeptides of SEQ ID NO: 3, 4, 5, 6 and 7, that are cleavable by polypeptides of SEQ ID NO: 8 and/or 9, does not reasonably provide enablement for any polypeptide less than 40 amino acids in length comprising a cleavage site for any aggrecanase wherein said site is located between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any polypeptide less than 40 amino acids in length and comprising a cleavage site for any aggrecanase between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

Providing any aggrecanase covered by the scope of the invention requires cloning extremely large number of genes originating from any animal or gene bank.

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The genes should be subsequently, expressed and the encoded polypeptides tested for aggrecanase activity using a standard substrate, i.e., the aggrecan fragment of more than 40 amino acids comprising residues Glu373-Ala374. After being successful in these lengthy and tedious procedures that are out of realm of the routine experimentation in the art, one skilled in the art has to design the polypeptides with the desired characteristics and test them for being a substrate for any of aggrecanases.

While providing a polypeptide with claimed characteristics as a candidate substrate for an aggrecanase, has certain probability of success, Applicants' own investigations indicate that this probability is low. Applicants' data presented in Figure 2 provide an evidence that in case of aggrecanase of SEQ ID NO: 8 the probability is about 6% (6/56, taking those polypeptides for which the activity of cleaving is about 0.1 units) and in the case of aggrecanase of SEQ ID NO: 9 is even less, about 7% (4/56, taking into account those polypeptides for which the activity of cleaving is about 0.5 units). The probability of finding a peptide with the described characteristics that is a substrate for any aggrecanase is even less, because Applicants' own data from Fig. 2 indicate that the probability of finding peptide that is a substrate for only two aggrecanases (SEQ ID NO: 8 and 9) is about 3/56, i.e., about 3%.

Examiner concludes that without the further guidance on the part of Applicants in regarding the structure of aggrecanases and their substrates used in the claimed method experimentation left to those in the art is improperly extensive and undue.

4. Conclusion

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All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

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